Assessment of volume status and fluid responsiveness in intensive care

Before completing this tutorial please answer the following MCQs:

1. Regarding the Frank-Starling mechanism, which statement is true?
   - An increase in preload will shift the curve up and to the left.
   - The cardiac output continuously increases as the preload increases.
   - An increase in afterload shifts the curve down and to the right.
   - If the inotropy increases, the stroke volume will decrease for the same preload.

2. Each 1 litre of positive fluid balance during the first 72 h of ICU stay was associated with an increase mortality of:
   - 5%
   - 10%
   - 30%
   - 50%

3. Regarding static measurements of volume status, which statement is true:
   - CVP depends solely on venous return to the right heart.
   - A low CVP is a reliable marker of hypovolaemia.
   - In ideal circumstances, PCWP is proportional to the LV preload.
   - Echocardiographic parameters have been validated to predict fluid response in critical patients.

4. Regarding dynamic measurements of fluid status, which statement is false:
   - Dynamic measurements are affected by the changes in intrathoracic pressure during respiration.
   - The respiratory variation of SV is more pronounced in the flat portion of the Frank-Starling curve.
   - Pulse pressure variation is more reliable than stroke volume variation at predicting fluid responsiveness.
   - Dynamic parameters can only be obtained with transoesophageal echocardiography.
5 Regarding passive leg raise, which statement is false:

- It is a quick and reversible way of increasing preload.
- It should be performed by elevating both lower limbs to 90°.
- It is not possible to perform in mechanically-ventilated patients.
- It is influenced by intra-abdominal pressure.

Key points:

- Accurate assessment of volume status as well as whether cardiac output will respond positively to a fluid challenge is a common albeit challenging task in the care of critically ill patients.
- The ability of clinical acumen to adequately assess fluid status is limited and should be combined with ancillary tests.
- Static pressure measurements, such as the CVP and PCWP, have little utility and should not be routinely used to assess volume status or fluid responsiveness.
- Newer dynamic measurements, like PPV and echocardiographic parameters, hold great promise for determining fluid status but often require sedation and invasive monitoring.
- Passive leg raise can provide useful information to complement clinical assessment in spontaneously breathing patients.
- Clinical judgement is required to interpret the results of volume measurements in the context of the individual patient.

Introduction

It is a typical morning intensive care round. There is a septic, mechanically ventilated patient, who remains hypotensive despite aggressive fluid therapy overnight. The patient is dependent on vasopressors to meet with the targets of ‘early goal directed therapy’. A lively debate ensues with someone advocating a fluid bolus, whilst someone else feels the patient is already overloaded. How can the conflict be resolved? How can volume status be accurately assessed?
The underlying principle: the Frank-Starling law

The Frank-Starling law describes the relationship between preload, mainly influenced by venous return, and contractility (Figure 1). It resulted from the joint work of two scientists: Otto Frank observed, using isolated frog hearts, that the strength of ventricular contraction was increased when the ventricle was stretched prior to contraction; later Ernest Starling and colleagues in the early 20th century found that increasing venous return to the heart, which increased the filling pressure (left ventricular end-diastolic pressure; LVEDP) of the ventricle, led to increased stroke volume (SV). Conversely, decreasing venous return decreased filling pressure and SV. This ventricular response to changes in venous return is intrinsic to the heart but it can be modified by extrinsic neurohumoral mechanisms. Therefore, the ventricle can operate on several Frank-Starling curves depending on the afterload and inotropic state, which is influenced by neurohumoral systems (e.g. noradrenaline, angiotensin-aldosterone, dopamine).

As shown in Figure 2, increasing afterload (the resistance against ventricular contraction) or decreasing inotropy (the contractility of the myocardium) shifts the curve down and to the right, which means that at a given preload (LVEDP) the ventricular response (SV) will be lower. On the contrary, decreasing afterload and increasing inotropy shifts the curve up and to the left, which means that at a given preload (LVEDP) the force generated by the ventricle and so the SV will be higher.

Figure 1 [left]: Frank-Starling curve (basal)
Figure 2 [right]: Multiple Frank-Starling curves in response to changes in afterload and inotropy
The underlying mechanisms for the increase in ventricular contraction with increased preload (LVEDP) are related to the degree of stretching of cardiac myocytes. There is an optimal sarcomere length in which force generation and thus ventricular contraction are maximal, which is at least partly explained by increased activation of contractile proteins.

Based on the Frank-Starling mechanism, pressure-volume loops can be created to depict how changes in venous return affect end-diastolic and end-systolic volumes (Figure 3). When venous return increases, there is increased filling of the ventricle along its passive pressure curve leading to an increase in LVEDV. If the ventricle now contracts at this increased preload, provided that afterload and inotropy remain constant, the ventricle empties to the same LVESV, which then results in an increase in SV (width of the pressure-volume loop). This demonstrates how a normal ventricle can match stroke volume to physiological increases in venous return; the loss of this response explains the inability of failing ventricles to cope with increases in preload.
Why is it important to assess intravascular volume?

Although aggressive fluid resuscitation targeted to central venous pressure (CVP) and physiological variables has been the mainstay of early goal directed therapy to reduce organ failure and improve survival in patients with severe sepsis and septic shock [1], more recent studies in critically ill patients have demonstrated that excessive fluid resuscitation and markedly positive net fluid balance is associated with higher rates of complications and increased mortality [2]. In a European multicentre observational study of patients admitted to the ICU, each 1 litre of positive fluid balance during the first 72 h of ICU stay was associated with a 10% increase in mortality after adjustments for other risk factors [3]. A more conservative fluid management strategy seems particularly beneficial for patients with acute lung injury in the ICU due to the detrimental effects of fluid overload on gas exchange [4]. Although both insufficient and excessive resuscitation are associated with worse clinical outcomes, most decisions regarding fluid therapy are still made empirically.

The two crucial questions in fluid resuscitation are: (1) what is the current state of the patient’s intravascular volume? and (2) if the patient receives continued fluid resuscitation or a fluid bolus, will physiological variables such as blood pressure, tissue perfusion, and urine output improve (i.e. is the patient fluid-responsive)?

History and examination

History and examination provide the earliest evidence of volume status (Table 1). The most reliable symptoms of volume overload are paroxysmal nocturnal dyspnoea, orthopnoea and peripheral oedema [5]. For blood-loss hypovolaemia, postural hypotension was the most useful physical finding but only for large blood losses (>1 litre). However, the accuracy of physical findings is more limited for non-blood loss related hypovolaemia, for which laboratory tests are required (Table 2)[6].

Chest radiograph and echocardiography

The daily chest X-ray (CXR) in the ICU is an established diagnostic tool to complement history and physical examination findings, and is commonly used to assess volume status. However, common CXR findings (e.g. venous redistribution, interstitial oedema) are highly variable and insensitive and more complex measurements like cardiac index and vascular pedicle width although more reliable are technically difficult [7, 8]. Therefore, the utility of physical findings and CXR to assess volume status is limited and so more sensitive and specific techniques are needed.
### Table 1: Clinical signs and symptoms of tissue hypoperfusion and shock [48]

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms or signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Altered mental status (dizziness, lethargy, coma)</td>
</tr>
<tr>
<td>Circulatory</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Tachycardia, arrhythmias, hypotension, new murmur</td>
</tr>
<tr>
<td>Systemic</td>
<td>Hypotension, decreased or increased jugular venous distension, narrow pulse</td>
</tr>
<tr>
<td></td>
<td>pressure</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnoea and dyspnoea</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria</td>
</tr>
<tr>
<td>Skin</td>
<td>Mottled, cool, clammy or warm (vasodilatory shock)</td>
</tr>
</tbody>
</table>

### Table 2: Biochemical parameters indicating tissue hypoperfusion [48]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine specific gravity</td>
<td>In CKD and AKI urine specific gravity is not reliable in the assessment of intravascular volume due to lack of renal concentrating ability</td>
</tr>
<tr>
<td>BUN/Cr</td>
<td>In prerenal state, BUN is absorbed in proximal tubules out of proportion to GFR and serum creatinine, increasing the BUN/Cr ratio. Caveats: steroid therapy and low muscle mass can increase the ratio and decreased protein intake can lower the ratio.</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>Urine sodium is high in ATN and diuretic therapy.</td>
</tr>
<tr>
<td>FeNa</td>
<td>Fractional excretion of sodium for differentiating prerenal state and renal hypoperfusion from AKI. Caveats: low FeNa is seen in contrast nephropathy, rhabdomyolysis, glomerulonephritis, vasculitis, ATN in setting of cirrhosis, and congestive heart failure. High FeNa is seen in AKI (e.g., ATN) and with diuretic use even in setting of shock.</td>
</tr>
<tr>
<td>FeUrea</td>
<td>High in ATN.</td>
</tr>
<tr>
<td>Serum lactate</td>
<td>Lactic clearance in shock is a better indicator of tissue perfusion and response to treatment than single measurement of serum lactate. Lactate clearance should be interpreted with caution in severe liver disease.</td>
</tr>
<tr>
<td>ScvO₂</td>
<td>Normal or high ScvO₂ does not necessarily indicate adequate perfusion and oxygen use or exclude the need for further fluid administration (e.g. impaired oxygen use due to mitochondrial dysfunction)</td>
</tr>
</tbody>
</table>
Static measurements:

Central venous pressure

Central venous pressure (CVP), obtained using a pressure transducer attached to a central venous catheter, is probably the most popular parameter used to guide fluid therapy in ICU, because it is simple, static and easy to interpret. In addition, randomized controlled trials (RCT) have used CVP to set targets for fluid therapy for instance in sepsis [1] and ARDS [4]. However, CVP does not predict whether the patient’s cardiac output (which depends on SV and HR) will increase in response to a fluid bolus [9, 10]. CVP is dependent on venous return (VR) to the heart, right ventricular compliance, peripheral venous tone, and posture, and the CVP is particularly unreliable in pulmonary vascular disease, right ventricular disease, patients with tense ascites, isolated left ventricular failure, and valvular heart disease. In patients with an intact sympathetic response to hypovolemia, the CVP may fall in response to fluid, as compensatory vasoconstriction is reduced [11]. Therefore, it is possible to have a low CVP and not be volume responsive, as well as have a high CVP and be volume responsive [12].

Pulmonary capillary wedge pressure (PCWP)

Pulmonary artery occlusion pressure or PCWP has been widely used to assess volume status and fluid responsiveness in the ICU and operating room because in ideal circumstances it is proportional to LVEDV/preload. However, most studies demonstrated a poor correlation with volume responsiveness, which might be due to changes in vascular and cardiac compliance, distribution of fluids in the various compartments of the cardiovascular system, and the compromised cardiac response to an increase in preload in critically ill patients [11, 13].

Echocardiography

There are several two-dimensional and Doppler flow measurements that can be obtained from transthoracic or transoesophageal echocardiography (TTE or TOE) that provide cardiac chamber volume assessment [14]. However, in the absence of baseline echocardiographic data, isolated measurements are hard to interpret due to individual variability, which compromises their usefulness in the assessment of preload and volume responsiveness.
Dynamic measurements

Dynamic measurements have been developed to overcome the limitations of static parameters to better discriminate between those patients who increase SV with fluid therapy ('fluid responders') and those who do not ('nonresponders'). The degree of variation of those dynamic parameters depends on the changes in intrathoracic pressure induced by spontaneous and mechanical ventilation [15]. Furthermore, the changes in RV and LV SV with respiration/ventilation are more pronounced on the steep ('volume responsive') compared with the flat portion of the Frank-Starling curve (that is, significant hypovolaemia results in more pronounced changes in arterial pressure during the respiratory cycle) [16].

Systolic pressure variation, SVV and PPV

For a given arterial compliance, the amplitude of the pulse pressure is directly related to SV. This makes SVV and PPV potentially more useful parameters over SPV as they are less affected by changes in diastolic pressure that affect the systolic pressure and could confound interpretation [17]. PPV is calculated by one of several techniques that calculate the difference between maximum and minimum pulse pressures during mechanical breaths, and SVV is computed through pulse contour analysis and computation of the area under the systolic portion of the arterial pressure curve.

There are several systems available to calculate SPS, SVV and PPV. Edwards Lifesciences (Irvine, CA) manufactures a system that calculates SVV (the Vigileo monitor and FloTrac sensor) by means of an arterial catheter and analysis of the arterial pressure waveform and it has been shown to optimise fluid management strategies [18, 19]. Another system for determining beat-to-beat measurement of CO along with the ability to ascertain SVV, PPV, and SPV is the LiDCO Plus System (LiDCO, Cambridge, UK). This calibrated system combines the LiDCO system for the measurement of CO using a lithium-based indicator dilution method along with the PulseCO system, which calculates continuous beat-to-beat analysis of CO [20]. Data derived from this system can be used to derive SVV, PPV, and SPV. However, evidence hitherto available is insufficient to either support or discard its routine use [21].

A less invasive alternative to these techniques is pulse pressure analysis during mechanical ventilation using dynamic changes in both the peak and amplitude of the pulse oximeter plethysmographic wave form. These volume changes in arterial vessels correlate with PPV and provide a good estimate of fluid responsiveness [22, 23].
Several studies have demonstrated the superior performance of PPV in comparison to SVV, perhaps because PPV is directly measured on an arterial-line tracing whilst SVV is calculated from pulse contour analysis [24, 25].

However, those parameters have only been validated in mechanically ventilated patients who were paralysed, which undermines the accuracy of extrapolations to spontaneously breathing patients [26, 27].

**Passive leg raise (PLR)**

PLR [28, 29] is a simple manoeuvre that can be performed in spontaneously breathing patients. This quick and reversible way of increasing preload offers a good estimation of cardiac response to volume with no risk of causing unnecessary harm, as it increases venous return to the heart without the need for an actual increase in total volume. Moreover, it does not require any sophisticated equipment or training. However, for reasons yet to be understood, it has never become standard of practice for assessment of volume status. From a more technical point of view, PLR ideally should be obtained by simultaneously elevating the lower limbs to 45° and lowering the patient into the supine position from a 45° degree semi-recumbent position. Several devices are available to translate the assessment of SV and CO to the increase preload induced by PLR. For instance, the FloTracVigileo (Edwards Lifesciences, Irvine, CA) system shows how SVV responds to PLR [30], whilst transpulmonary thermodilution (PICCO system, Pulsion Medical Systems, Munich, Germany) shows the effects of PLR on cardiac output with pulse pressure analysis [31]. A noninvasive alternative to those systems is the noninvasive CO monitor (NICOM, Cheetah Medical, Portland, OR), which allows continuous haemodynamic monitoring based on bioreactance [32] and can predict cardiac response to PLR or an IV fluid challenge [33, 34].

**Oesophageal Doppler**

Oesophageal Doppler monitoring, by means of a probe placed in the oesophagus through the nose or mouth, allows measuring aortic blood flow in the descending thoracic aorta and hence provides good estimates of SV and cardiac output [35]. However, the probe is poorly tolerated in awake patients and it needs to be refocused prior to each measurement, making it more suitable for repeated measurements than for continuous monitoring.

In the UK, NICE has approved the use of the CardioQ-ODM oesophageal doppler monitor in people who are having major surgery or people having surgery who would otherwise be monitored with a more invasive method [36]. The approval was granted
on the grounds that it reduces the use of central venous catheters, complications after surgery and the length of stay in hospital without increasing the need for readmission to hospital or repeat surgery. However, further evidence is required to fully clarify the actual benefit of oesophageal Doppler for predicting fluid responsiveness [37].

Echocardiography

Bedside transthoracic echocardiography has met with increased interest for the last years and it is now commonly used for volume assessment [38, 39]. Nevertheless, there is ongoing controversy on which measurements are better at predicting response to a fluid bolus. Inferior vena cava (IVC) diameter or the extent of respiratory cycle variation [16, 40, 41] together superior vena cava (SVC) collapsibility index [42] are the most often employed to assess fluid responsiveness. Respiratory SVC variation seems to have the best specificity and overall accuracy, whereas maximal Doppler velocity in the left ventricular outflow track has the best sensitivity for predicting fluid response [43]. However, those measurements cannot be obtained on a continuous basis and may be technically difficult due to body habitus. In addition, IVC diameter is influenced by intra-abdominal pressure and thus has limited use in patients post laparotomy or with suspected high intra-abdominal pressures. On the other hand, SVC measurements require TOE, which is logistically difficult to obtain in unstable, critically ill patients.

Bioimpedance vector analysis

Bioimpedance vector analysis is a new technique that is currently under investigation and appears promising as noninvasive, real-time measurement of static volume status [44]. It relies on the relative conduction of electrical current by different body tissues, including water. Although it might be useful in managing patients with volume overload [45-47], it is not able to differentiate between compartmentalised oedema and increased total body water. It is thus unable to assess intravascular volume and response to fluid therapy.

Conclusion

Early recognition and treatment of acute circulatory failure and tissue hypoperfusion are crucial in the management of critically ill patients but accurate assessment of intravascular volume remains one of the most challenging tasks for clinicians. Accurate identification of patients who would benefit from fluid resuscitation is paramount to optimise haemodynamic parameters and avoid the deleterious consequences of fluid
overload, particularly pulmonary oedema, in patients for whom inotropic and/or vasopressor support would be preferable.

Although clinical experience and acumen remain the cornerstone of assessment of volume status, additional diagnostic tests are useful to support or refute clinical assessments (Table 3). Static pressure measurements have been progressively replaced by newer dynamic measurements. Although the latter are more accurate at predicting response to fluid therapy, the common requirement for sophisticated equipment and training as well as invasiveness preclude more routine use [48]. None of the methods hitherto available has demonstrated enough accuracy and reliability to override clinical judgement, considering the context of each individual patient.
### Table 3: Summary of volume assessment tools [49]

<table>
<thead>
<tr>
<th>Method</th>
<th>Invasive or Noninvasive</th>
<th>Static or Dynamic</th>
<th>Predict fluid responsiveness</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical findings</td>
<td>Noninvasive</td>
<td>Static</td>
<td>No</td>
<td>Of limited value with poor correlation with invasive pressure measurements</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Noninvasive</td>
<td>Static and dynamic</td>
<td>Yes</td>
<td>Of limited value but serial examinations may detect changes in organ perfusion</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Noninvasive</td>
<td>Static</td>
<td>No</td>
<td>Requires use of standardized measures of vascular pedicle width and cardiothoracic ratio. Serial chest X-ray may be helpful in determining effects of fluid therapy</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>Invasive</td>
<td>Static</td>
<td>No</td>
<td>Poor correlation with fluid responsiveness</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure</td>
<td>Invasive</td>
<td>Static</td>
<td>No</td>
<td>Poor correlation with fluid responsiveness</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Noninvasive</td>
<td>Static</td>
<td>No</td>
<td>Single measures of cardiac chamber volume hard to assess. Serial measures may be helpful</td>
</tr>
<tr>
<td>Stroke volume or pulse pressure variation</td>
<td>Invasive (pulse oximeter method in noninvasive)</td>
<td>Dynamic</td>
<td>Yes</td>
<td>Requires sedated, mechanically ventilated patient</td>
</tr>
<tr>
<td>Esophageal doppler</td>
<td>Invasive</td>
<td>Dynamic</td>
<td>Yes</td>
<td>Not useful for continuous measurements</td>
</tr>
<tr>
<td>Vena cava diameter</td>
<td>Noninvasive</td>
<td>Dynamic</td>
<td>Yes</td>
<td>Body habitus dependent</td>
</tr>
<tr>
<td>Passive leg raising</td>
<td>Noninvasive (bioreactance, end-tidal CO₂)</td>
<td>Dynamic</td>
<td>Yes</td>
<td>Unreliable with intra-abdominal hypertension</td>
</tr>
<tr>
<td>End-expiratory occlusion</td>
<td>Invasive (FloTrac or PICCO or LIDOO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioimpedance</td>
<td>Noninvasive</td>
<td>Static</td>
<td>No</td>
<td>Not able to assess intravascular volume</td>
</tr>
</tbody>
</table>
Answers to MCQs:

1 FFTF
2 FTFF
3 FFTF
4 FTFF
5 FTFF

References

9 Durairaj L, Schmidt GA Fluid therapy in resuscitated sepsis: less is more. Chest 2008; 133: 252-63.

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